UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/173,864	10/16/98	IVARIE R	24011-0002

HM22/0425

HELLER EHRMAN WHITE & MCAULIFFE
525 UNIVERSITY AVENUE
PALO ALTO CA 94301-1900

EXAMINER
KAUSHAL,S

ART UNIT	PAPER NUMBER
1633	18

DATE MAILED: 04/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/173,864	IVARIE ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- Th MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21,25,27,29,33-35,41-49 and 52-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21,25,27,29,33-35,41-49 and 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 02/13/01 and Dr. Jeffrey Rapp's declaration under 37CFR 1.32 have been acknowledged. Claims 50 and 51 are canceled. Claims 19, 21, 25, 27, 29, 33-35, 41-49, 52-57 are pending in this application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 19, 21, 27, 29, 33-35, 42-49, 52-55 and 57 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use the invention**, for the same reasons of record as set forth in the official action mailed on Paper No 12, 8/8/00.

The applicant argues that Dr. Rapp declaration is presented to address the enablement issues raised in the earlier office action (8/8/00) and at the interview of Dec 19, 2000. The applicant further argues that the procedure has been successfully practiced to express various exogenous proteins in the serum of transgenic birds (response, page 3, para. 1). The applicant further states that todate both hIFN and β-lac have been found in egg white material of G2 hens and it is expected that similar results will be obtained for hEPO and hGM-CSF when those experiments are completed (response, page 3, para. 1, line 12-13). The applicant concluded that invention as claimed does not require undue amount of experimentation in view of applicant's disclosure (response, page 3-4).

Dr. Jeffrey Rapp's declaration under 37CFR 1.32 states that the out of 1597 offsprings one rooster was found transgenic "Alphie" whose G2 offsprings hens produces an average of 900

nanograms/ml hIFN in the egg white material (declaration, page 7, para 2). The declaration further states that G1 roster 4133 and his progeny express from about 0.6-1.2 ug/ml of β-lactamase in egg white from the eggs of hens sired by the 4133 roster (declaration, page 8, para.2).

However, this not found fully persuasive because the full scope of the invention as claimed is not supported by Dr. Jeffrey Rapp's declaration as submitted.

- The invention as claimed encompass any and all transgenic birds *(chicken, pigeons, ducks, turkey, crows and sparrows etc*) wherein the exogenous transgene is expressed in the tubular gland cells of the avian oviduct.

- The invention as claimed further encompass a transgenic egg and method of producing an avian egg from a transgenic avian, which contains any and all exogenous protein *(HGH, antitrypsin, ...insulin, EPO. GM-CSF,..... feed adetive enzymes ...Chymotrypsin etc*), wherein the protein is secreted into the oviduct lumen so that the protein is deposited in the egg white.

- The invention as claimed encompass a method of producing an exogenous protein in an avian oviduct by making a transgenic avian, wherein the protein is expressed in tubular gland cells of transgenic avian. In addition, the invention as claimed further encompass any and all transgenic birds having a transgene in the germ line tissue of the tubular gland cells of its magnum.

- The invention as claimed further encompass a transgenic bird expressing an exogenous gene in the tubular gland cells of its magnums, wherein the protein is deposited in into the egg white of an egg of that bird.

The specification teaches making of an ALV-base retroviral vector wherein the CMV promoter derives the expression of b-lactamase (example-1 and 2). The specification teaches production of chimeric chickens transducing stage X embryos with NLB-CMV-BL retroviral particles (page 34, line 10-15). The specification further teaches the detection of b-lactamase activity in the egg white of chimeric chickens (page 36 table-1). The specification fails to show even a single transgenic founder obtained from chimeric chickens, capable of producing a transgenic progeny expressing the any exogenous protein (as claimed) in oviduct and/or eggs in any and all offspring.

At best Dr. Dr. Jeffrey Rapp's declaration discloses a transgenic rooster "Alphie" whose G2 offsprings hens produces an average of 900 nanograms/ml hIFN in the egg white (declaration, page 7, para 2). In addition the addition the declaration further discloses a trangenic rooster 4133 whose G2 progeny express an average of 0.6-1.2 ug/ml of b-lactamase in egg white (declaration, page 8, para.2). The declaration teaches the systemic expression of hIFN and b-lactamase and fails to demonstrate tissue specific (*oviduct, tubular glands or magnum*) expression of any and all transgenes as claimed (*HGH, antitrypsin, ...insulin, EPO. GM-CSF,..... feed additive enzymes ...Chymotrypsin etc).* Therefore, the declaration as filed does not encompass all aspects of the invention as claimed.

As stated in the earlier office action, the art at the time of filing clearly states that the making of transgenic birds is highly unpredictable because the complexities of egg formation make the earliest stages of chick-embryo development relatively in-accessible (Sang TIBTECH 12:415-420, 1994, page 415, col.2 para.2). Furthermore, the making of chimeric birds is technically demanding as its requires the development of methods that enhances the survival of embryonic cells and an increase in frequency of chromosomal integration of injected DNA (Sang, page 416, col.1 para.3). Furthermore, ex-vivo transfection of blastodermal cells and reimplantation into an egg has not show to transmit the transgene through germ lines. In addition, the development of chicken embryonic stem cells that can be grown for longer periods in culture to allow the targeted recombination events is highly unpredictable (Sang page 417, col.1 para. 1-2). Furthermore, it is unclear how a particular transgene would effect the

development of mature birds and the production of transgenic eggs. For example, over expression system expression of insulin (as claimed, claim 41) would severely affect the development of chicks to eggs laying birds due to hypoglycemia. Therefore, considering the unpredictable nature of avian transgenic art, the declaration and the specification as filed fails to support the full scope of invention as claimed. Since to make and test is not the standard for enablement, one skill in the art would have to engage in excessive and undue amount of experimentation.

Furthermore, replication defective retroviral vector has been used to obtain germ line transmission of transgenes resulting in a wide variety of tissues, however tissue-specific expression has not been achieved (Simkiss, Transgenic birds, animals with novel genes, Mclean ed, Cambridge Univ.Press NY pages 106-137, 1994, see paragraph bridging pages 118-119). The specification fails to show the expression of any exogenous protein in the tubular gland cells of oviduct or magnum tissue of any and all birds. The specification only provided a prophetic example in fig-6, which illustrates magnum-specific gene expression in magnum and non-magnum cells (page 13, line 9-13).

Thus, in view of lack of specific guidance in the specification and the declaration, and considering the state of the art, the skilled artesian at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making any and all transgenic birds *(chicken, pigeons, ducks, turkey, crows and sparrows etc)* and eggs thereof, wherein the eggs contain any and all exogenous protein of interest *(HGH, antitrypsin, ...insulin, EPO. GM-CSF,..... feed adetive enzymes ...Chymotrypsin etc)*. In addition, experimentation required would further include the development of transgenic birds wherein the expression of an exogenous protein of interest is tissue specific (*oviduct, tubular glands or magnum)*.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 25, 41 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Bosselman et al (US 5162215, 1992). Bosselman teaches the micro-injection of a replication-defective REV-derived retroviral vector in side the egg around the blastoderm. After the injection the eggs are sealed and incubated to form chicks (col/8 line 45-66). The cited art further teaches the transfer of nucleic acid sequences encoding desirable protein products like human serum albumin, alpha1-antitrypsin, blood clotting proteins (factor VIII) and hematopoietic growth factors (EPO, G-CSF, LGF) to make transgenic chickens and eggs thereof, wherein the egg contain a desirable protein product (col.6 line 8-17).

The invention of instant claims is drawn to "an intact egg of an avian species containing protein exogenous to an egg of avian species" (see claim 25). The method disclosed by Bosselman et al encompasses an intact egg because after retroviral injection the contents of the injected eggs are intact because upon incubation the eggs leads to the formation of chickens. Furthermore, the injected retroviral vector consists of proteins that are exogenous to an egg of any avian species. Therefore the invention as claimed clearly anticipated by Bosselman et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bosselman et al as applied to claim 25 and 41 above, and further in view of Sekellick et al (WO95/11302, 1995)

Bosselman teaches the micro-injection of a replication-defective REV-derived retroviral vector in side the egg around the blastoderm. After the injection the eggs are sealed and incubated to form chicks (col/8 line 45-66). The cited art further teaches the transfer of nucleic acid sequences encoding desirable protein products like human serum albumin, alpha1-antitrypsin, blood clotting proteins (factor VIII) and hematopoietic growth factors (EPO, G-CSF, LGF) to make transgenic chickens and eggs thereof, wherein the egg contain a desirable protein product (col.6 line 8-17).

The invention of instant claims is drawn to "an intact egg of an avian species containing protein exogenous to an egg of avian species" (see claim 25). The method disclosed by Bosselman et al encompasses an intact egg because after retroviral injection the contents of the injected eggs are intact because upon incubation the eggs leads to the formation of chickens. Furthermore, the injected retroviral vector consists of proteins that are exogenous to an egg of any avian species.

However Bosselman et al does not teaches the transfer of nucleic acid encoding an interferon to make transgenic chickens and eggs containing an exogenous interferon.

Sekellick et al teaches the chicken interferon gene, which can be used to make a transgenic fowl (page 4 line 8-24).

Thus, it would have been obvious to one ordinary skill in the art at the time of filing to modify a replication-defective retroviral vector to encode an interferon gene (as taught by Sekellick et al) and micro inject the modified retroviral vectors into an intact eggs as taught by Bosselman et al. One would have been motivated to produce an interferon in an intact egg because an interferon is the gene of interest that is useful in protecting and treating animals and humans from viral and other diseases.

Conclusion

No claims are allowed.

Claims 25, 41 and 56 are rejected

Claims 19, 21, 27, 29, 33-35, 42-49, 52-55 and 57 are free of prior art. The art at the time of filing does not teach or suggest the making of a transgenic bird wherein the exogenous gene is expressed in the tubular gland cells of an avian oviduct and the protein encoded by the transgene is deposited into eggs.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are advised to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and a COPY OF ALL THE PENDING CLAIMS IS REQUESTED to facilitate further examination.

S. Kaushal,
PATENT EXAMINER
AU 1633